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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,039	07/30/2001	Yong Mi Choi-Sledeski	P24450-E US1	3370

7590 12/30/2005

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,039	CHOI-SLEDESKI ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In the reply of 9-26-05, applicants have elected with traverse the subject matter of group 16 and the species in Example 48.

The traversal is on the grounds that the compounds have a substantial structural feature of the formula as recited in claim 35, and that the compounds have a common utility (i.e., inhibiting an activity of Factor Xa).

Applicant asserted that the original Ar^1 has been replaced with a *bicycle* having ring atoms of A_1, A_2, A_3 and A_4. Thus, there is unity of invention.

Applicant's traversal is not found persuasive for the following reasons:

- The *bicyclic* core of A_1-A_4 can vary in structure depending on the position of A_1-A_3. The core of *pyrrolo[2,3-b]pyridine* is definitely not obvious over the core of *pyrrolo[3,2-c]pyridine,* nor it is obvious over *pyrrolo[2,3-c]pyridine*. Therefore, the bicyclic core is not a special technical feature that is common to compounds of all the groups.
- Furthermore, variables R_1 and R_2 represent a large number of functional groups and ring systems. The combination of which would definitely set apart compounds of one group from those of the others.
- Although all groups share the *pyrrolidinone* ring, such a ring alone does not sufficiently define the invention, and is not a contribution to the art.

- Therefore, it is the combination of at least *pyrrolidinone*, *bicyclic core,* and R_2 that gives compounds in each group their unique physical and chemical properties as well as biological activity.

Because Group 16 was indicated with further restriction, it is therefore, divided as below:

Group 16a: Claims 35-41 (in part) drawn to a pharmaceutical composition, and a method of treatment using a compound of the formula recited in claim 35 wherein:

- The bicyclic system having A_1-A_4 is *pyrrolo[2,3-c]pyridine*;
- R_2 is $R_3S(O)_p$; p = 2;
- R_3 is *thieno[3,2-b]pyridine*
- X_3 and one of X_1 and X_{1a} do not form a ring (i.e., no fused pyrrolidinone).

In combination with at least one other agent selected from diagnostic agents, cardioprotective agents, direct thrombin inhibiting agents, anticoagulant agents, antiplatelet agents and fibrinoloytic agents; classified in class 514, and 546, various subsclasses depending on substituents.

Group 16b: Claims 35-41 (in part) drawn to a pharmaceutical composition and a method of treatment using a compound of the formula recited in claim 35 wherein:

- The bicyclic system having A_1-A_4 is **not** *pyrrolo[2,3-b]pyridine, pyrrolo[3,2-c]pyridine*, or *pyrrolo[2,3-c]pyridine*;
- R_2 is **not** $R_3S(O)_p$; p = 2;
- R_3 is **not** *thieno[3,2-b]pyridine*;

In combination with at least one other agent selected from diagnostic agents, cardioprotective agents, direct thrombin inhibiting agents, anticoagulant agents, antiplatelet agents and fibrinoloytic agents; classified in class 514, and 546, various subsclasses depending on substituents.

The elected species falls within Group 16a, and thus, claims 35-41 are considered to the extent of the subject matter in Group 16a.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 35-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 35 recites the disorder as "*a physiological disorder capable of being modulated by inhibiting an activity of Factor Xa...*" which has indefinite metes and bounds because it reads on a disorder with too little clotting (e.g., hemophilia), and also a disorder with too much clotting (e.g., embolism). Besides, the specification associates factor Xa with more diseases than just blood coagulation. Thus, it is unclear what other diseases are intended in the method of claim 35.

b. Claims 35 and 39 recite the positions of Z which is "positions 2 to 7" on the pyrrolopyridine ring. However, it is noted that the pyrrolopyridine ring is not numbered the way recognized by the art. That is, as exemplified by the elected species, the 2-position is on the pyrrolo ring, and not on the pyridine ring. Such an unconventional way of numbering appears to be inconsistent with the way recognized by the art.

c. Claim 38 lacks antecedent basis because it depends on claim 35, but recites "prodrugs, derivatives and analogs thereof" which are not recited in claim 35.

d. Claim 39 is a pharmaceutical composition claim comprising additional therapeutic agent(s). However, it is not clear if the additional agent(s) are formulated together (in a tablet, capsule or injectable) with the claimed compound, or if it is in separate formulations, but is given at the same time (e.g, separate tablets in the same blister pak).

e. Claims 36-38, 40 and 41 are rejected as being dependent on either claim 35 or 39, and carrying over the indefinite limitations.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Enablement:** Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 35 recites: "A method for treating...a physiological disorder capable of being modulated by inhibiting an activity of Factor Xa comprising administering to the patient a therapeutically effective amount of a pyrrolopyridine compound having the structure...wherein said compound is administered in combination with at least one other agent selected from diagnositic agents, cardioprotective agents, direct thrombin inhibiting agents, anticoagulant agens, antiplatelet agents, and fibrinoloytic agents."

The action intended by the inhibition of Factor Xa includes more than anticoagulant therapy. According to the specification, such an action includes "*chronic and degenerative diseases as arthritis, cancer, atherosclerosis, restenosis post coronary angioplasty and Alzheimer's disease...*" Thus, not only claim 35 recites broad scope of compounds, but also a broad scope of diseases as well as additional agents. Therefore, the scope of claim 35 is unduly broad.

Claims 36-38 depend on claim 35, and recite specific additional agents. However, their scopes are still unduly broad in terms of the claimed compounds, and diseases related to Factor Xa.

Like claim 35, claim 39 recites a pharmaceutical composition comprising the claimed compounds and "*at least one other agent selected from diagnostic agents, cardioprotective agents, direct thrombin inhibiting agents, anticoagulant agents, antiplatelet agents and fibrinoloytic agents.*" The scope of the compounds recited in claim 39 is just as broad as that recited in claim 35. With the combination of so many agents, the scope of claim 39 is unduly broad.

Claims 40 and 41 depend on claim 39, and recite specific additional agents, but still has the broad scope of the compounds. Therefore, the scopes of claims 40 and 41 are unduly broad as well.

The amount of direction or guidance presented:

Although the specification provides the guidance for making the claimed *pyrrolo[2,3-c]pyridine* compounds, as exemplified by the elected species in Example 48. However,

regarding the activity of such a compound as inhibitor of Factor Xa, the specification does not provide any IC_{50} value of such a compound. The specification only describes bioassay procedures without disclosing any tested *pyrrolo[2,3-c]pyridine* compounds. The only compound actually tested was a compound of substituted *1,6-diaminoisoquinoline*. Although *isoquinoline* is a bicycle, its structure is not equivalent to that of *pyrrolo[2,3-c]pyridine*. Thus, the activity of isoquinoline cannot be extrapolated to that of *pyrrolo[2,3-c]pyridine*. As for the combination of the claimed compounds and other agents, the specification does not teach how the claimed compounds can be combined as at what dosage. Thus, the specification fails to provide sufficient guidance for one skilled in the art to make such a pharmaceutical composition as recited in claims 39-41, and use it in a broad method as recited in claims 35-38.

The state of the prior art:

Although anticoagulant agents can often be combined in the clinical setting, such a combination is often done for a short term (e.g., post-op telemetry), and with close monitoring of the prothrombin time. Some anticoagulant agents can interfere by displacing or competing with each other for protein binding, and thus, could alter the bioavailability of each other. For example, warfarin is known to alter other drug's bioavailability by competing for protein binding. While blood clot does not have a desirable effect, too little clotting could lead to hemophilia, which could be just as detrimental.

Furthermore, as evident by the teachings of **Baker et. al.** (US 5,854,268), and **Chambers et. al.** (US 5,604,240), the compounds of *pyrrolo[2,3-c]pyridine* have the activity of selective agonists of 5-HT_1 receptors, and not inhibitors of Factor Xa. Thus, the current practice of

medicine and state of the prior arts do not seem to support the pharmaceutical composition and method of treatment recited in claims 35-41.

The relative skill of those in the art:

Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula I. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Once an effective compound is identified, the skilled clinician would have to evaluate the combination of said compound with any of the additional agents listed in claims 35-41. Given a large Markush group of the claimed formula I, and the multiple combinations, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only describes bioassays without indicating any tested compounds of *pyrrolo[2,3-c]pyridine.* However, said description alone does not adequately guide the skilled clinician in the treatment of diseases that are allegedly related to Factor Xa which includes cancer, and Alzheimer's disease. Thus, with such a limited teaching, the skilled clinician would have to carry out undue experimentation to make a pharmaceutical composition by combining agents as recited in claims 39-41, and use it in the methods recited in claims 35-38.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Tamthom N. Truong
Examiner
Art Unit 1624

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12-11-05